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THE HABIT OF GROWTH.

AN INTRODUCTION TO A DISCUSSION UPON CARCINOMA AT THE MONTREAL MEDICO-CHIRURGICAL SOCIETY, DECEMBER 13TH, 1895.

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AN INTRODUCTION TO A DISCUSSION UPON CARCINOMA AT THE MONTREAL MEDICO-CHIRURGICAL SOCIETY, DECEMBER 13TH, 1895.

By J. George Adami, M.A., M.D.

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Frankly, gentlemen, it is impossible to do anything approaching to a discussion of the cause, progress and histological characters of cancerous growths in the time allotted to each of this evening's speakers, and I am bound, therefore, to select one single aspect of the subject for treatment, and even then can at the most touch rather than treat it.

Perhaps that which is of most general and present interest in connection with cancer, both from the point of the pure pathologist and from the standpoint also of the practical man, is the question of the causation of cancer. I say from the point of view of the man in practice, because once the cause of cancer is surely established it is generally held that prevention will be possible. This is the general hope, but for myself I am a little doubtful as to whether this really follows. I am not quite sure that when we establish satisfactorily the ætiology we shall find matters so simple that we can readily abolish or prevent the cause. Even if the condition be of a parasitic development, even if we are able to cultivate the parasite outside the body, and thus gain an intimate knowledge of its life history, I am not wholly hopeful that we can assume upon the analogy of modern bacteriological achievements and feel assured that eventually we can find means of arresting the growth of the parasite, and so of arresting the cancerous process, for, as I shall proceed to show, the *modus*

operandi of the parasite must differ essentially from that of the micro-organisms of ordinary zymotic disease. At the present time the most that can honestly be said with regard to the results of the investigations into the parasitology of cancer is that those investigations have revealed the occasional presence in the cancer cells of a series of very curious bodies. These bodies may be of the nature of sporozoa, they may with perhaps equal plausibility be regarded as the results of endogenous cell degeneration. So long ago as 1889–90 I gave out and demonstrated to my morbid histology class at Cambridge sections of a cancer of the scrotum showing these bodies. I am as much in doubt as to the nature of these bodies to-day as I was then. I leave it to Dr. Martin to bring before the Society the main results of the observations that have been made in this subject so far.

But it seems to me that even if we grant that cancer is caused by this parasite, we have not arrived very much further. In the first place, in all other parasitic and microbic diseases with which we are acquainted, general infection is brought about by the conveyance of the *microbe* from the primary seat of growth to other regions of the body by the lymph or the blood stream. In cancer general infection (a term which in consequence I am inclined to dislike seeing used in this connection, I prefer "metastasis") is essentially associated with a totally different process, namely, the conveyance of *tissue cells*. It is the cells carried to other regions by the lymph or the blood stream that there proliferate, and the secondary growths are in the oldest and strictest sense colonial. Just as the old Greek colonies were established by members of a community who migrated to a distance and there founded a new community of like constitution to the old, but wholly separate and owing no allegiance, so is it with the metastatic cancer growths. Even if in these migrating cells parasites be present, it must be admitted that we are dealing with a new type of infection wholly distinct from that induced by the tubercle bacillus, for example, and as a consequence we cannot predicate that the laws determining the prevention of one will determine the prevention of the other.

In the second place, granting that parasites bear an ætiological relation to cancer, we are still left in the dark as to why parasites induce certain cells of the body to take on a functionless and heterotopic growth. At most we acknowledge that an obscure organism originates aberrant vital processes on the part of sundry cells ; and inasmuch as similar aberrant vital processes are known to take place in other cells without there being any suggestion of similar parasites being present, we are led, I think harmfully, to separate off sharply

conditions which are related, we are led to neglect the attempt to find some common cause for all these conditions, we are led to separate sharply the malignant epithelial growths (I use this term in its broadest sense) from the malignant connective tissue growths; or if this be denied, and the sarcomata be accepted also as of parasitic causation, we are, at least, led to separate all malignant growths from all benign growths; we are conducted, that is, to an *impasse*. For this may be definitely accepted that certain benign growths are wholly unassociated with the presence of any parasite. Take, for example, the little lamellar fibromata to be seen upon the capsule of the spleen, or take the papillomatous overgrowth of the mucosa at the edge of a chronic intestinal ulcer, take the long finger-like down growths of epithelium at the boundary of a chronic ulcer, or the bony overgrowth upon the inner side of the femurs of cavalry soldiers. In all these cases chronic irritation is absolutely sufficient to explain the developments, yet no distinction can well be drawn between these chronic inflammatory hypertrophies and other forms of benign tumours. We must, then, logically admit that functionless and heterotopic cell hyperplasia can be induced without parasitic association; and inasmuch as the benign may pass imperceptibly into malignant growths, and inasmuch as we can, for example, come across lipomata showing transition into sarcomata, or fibromyomata doing exactly the same, as again we can, in thyroid, encounter what are certainly benign growths—adenomata (the so-called fœtal adenoma)—possessing all the histological characters of carcinomata, the only conclusion to be reached is that a study of the presumed parasite is calculated to lead us only a very little distance.

We must seek deeper than these suppositious parasites if we wish to discover what lies at the bottom of all malignant tumour growth, aye, of all functionless cell proliferation.

Now, that I may prepare you for the train of reasoning upon which I am about to embark, and that you may throughout the ensuing argument see whither it is tending, let me here state the conclusion at which I have thus far arrived from a study of neoplasms and not a little consideration concerning their characters and relationships. Briefly, I cannot but hold that the one fundamental phenomen underlying the development of cancerous and other neoplasms is the assumption of a habit of growth, a habit of rapid cell division independent of external stimulus on the part of certain cells in one or other region of the body.

The power of growth and multiplication is not, it must be borne in mind, something new to the cell. Every cell in the body, we may

safely say, either possesses or has possessed it. In every tissue, to the end of the life of that tissue, there is a constant, even if slow death of certain cells and replacement by cells of the same order, derived by proliferation of cells of that order. There is latent, that is to say, in all the living cells of the body a capacity for multiplication requiring only the necessary stimulus to call it into play. The habit of growth to which I have referred above is an exaggeration, or more exactly, a calling into full activity of this latent capacity.

This latent capacity for growth is much more intense in the vegetable kingdom, and numerous examples might be given in illustration. I need only remind you that if you nip off a piece of a begonia leaf, and place it under favourable conditions, that piece will develop into a complete plant. The cells of this leaf, highly differentiated as it is, have the latent power of orderly proliferation to such an extent that they can reproduce the whole plant.

Among the lower animals the same property is equally well marked. Cut a hydra into, I believe it may be said, almost as many parts as there are cells, and, provided that healthy and intact cells are left in the sections, each portion will develop into a complete hydra. The latent capacity for growth is such that each cell appears to have the potentiality not simply to produce cells of like order, but to reproduce the whole animal.

Ascend higher in the scale, and the latent capacity becomes more limited. In the crustacea for example, the potentiality is restrained to the reproduction of lost parts. Here the cells of various tissues proliferate harmoniously, and every tissue of the lost part is reproduced in proper proportion. Ascend yet higher, and the latent capacity is yet further restricted ; so that in man we observe the following, namely, that only the cells of certain relatively simple tissues possess to any marked degree the power of complete reproduction.

It may be said that all this is trite and commonplace, and it may be asked what it has to do with the pathology of carcinoma. Well, the recapitulation is valuable to this extent that it helps to impress upon us the proliferative capacity of the cells of the body, and the limitations to that capacity in the higher animals. As a matter of fact, it is only in the higher animals in which these limitations have been impressed upon the cells that malignant growth is possible and is found. In lower animals any stimulus to cell proliferation leads to reproduction either of the whole individual or of a complex of tissues

Recognising, then, the existence of this latent power of proliferation on the part of cells with the limitations that I have mentioned,

let me pass on forthwith to its bearing upon cancer formation, leaving aside, from lack of time, any consideration of the development of histoid tumours, even though I do this at the risk of being accused of passing by what is difficult to explain.

While in man we observe, as I have above stated, that only certain of the simpler tissues exhibit any marked power of proliferation leading to complete reproduction, the latent capacity for growth is present all the same, and we notice the appearance of a further and allied phenomenon. We see that under suitable irritation the cells of these higher tissues have not lost entirely their capacity for growth, only that capacity results in a development along somewhat different lines. What I mean can best be studied by observing the conduct of individual units of these higher tissues, either in the attempt at restoration of a muscle or nerve after section, or again, by a study of the processes occurring in glandular structures during the course of an inflammation that is not too intense. Severe inflammation leading, as it does, to active cell destruction is outside our purpose. Now, the most prominent characteristic of a nerve or muscle fibre present in the attempt at recovery after injury is the multiplication of the nuclei of each unit, a multiplication often regarded and spoken of as a degeneration, and indeed not unfrequently such multiplication precedes the actual disintegration of the unit. This multiplication, which I have elsewhere spoken of as "reversionary degeneration," is, I hold, an indication of a reversion to a more primitive type of cell, and indeed in the case of muscle Metchnikoff and others have shown that the individual nuclei resulting from this nuclear division may surround themselves with protoplasm and may pass away as simple embryonic cells, so that the whole muscle fibre becomes completely disintegrated. The process here is one of what may be also termed vital disintegration. The same principle that is shown here is to be seen at work in glandular structures. Take, for example, a case of parenchymatous nephritis. If this be acute the cells of the tubules swell up, show vacuolation and other signs of acute degeneration of the cell substance, with failure of the nuclei to stain properly (or to put it in other words, diminution of the chromatin of their nuclei), and the cells are cast off. With a lesser degree of inflammation the process is very different; we find here that the cells proliferate, but at the same time these new cells do not show the full adult character, their nuclei it is true stain intensely, but their bodies are small and cubical, their characters become more nearly allied to those of the cells in the developing kidney.

Or take the liver. Here in chronic inflammation we find the same

rule to obtain. If we study the comparative anatomy and the development of this organ we discover that it has arisen from a collection of separate acini or finger-like gland follicles. In the adult liver it is impossible to convince oneself of this fact; the cells seem to be arranged essentially in lobules around the branches of the hepatic vein; nevertheless the bile capillaries represent the lumina of the original or primitive gland follicles, and with chronic inflammation, as we see in case after case of cirrhosis, at the periphery of the lobules, the liver cells show the tendency to proliferation, with associated diminution in size; their nuclei stain as intensely as do those of neoplasms, so full are they of chromatin, and these small embryonic cells arrange themselves in a tubular manner, so that we have the appearance of numerous irregular winding ducts running through the new connective tissue formation at the periphery of the lobules—a reversion towards the primitive structure.

Still more instructive is the condition seen in the lung in chronic inflammation. In any case of chronic interstitial pneumonia [this term interstitial pneumonia is unsatisfactory, and a better one is chronic productive pneumonia, for the inflammation affects the parenchyma equally with the interstitial substance]—in any such case, I say, we observe that the result of continued inflammation is to lead to a modification of the epithelium lining the alveoli, so that instead of this being flattened and indistinguishable it is represented by a layer of small cubical cells in all respects resembling the cells lining future air sacs in the lung of the embryo.

In all these cases, therefore, we see this law holding good, that with chronic irritation of moderate intensity the cells of highly organized tissues tend to proliferate and to assume a more embryonic type. So true is this that time and again we pathologists are completely at a loss to give a full diagnosis. We receive from the gynæcologists, for example, scrapings from a womb with a history that there has been long-continued endometritis, and cancer is suspected. We receive from the surgeons portions of tissue taken from the edges of chronic ulcers, and are asked to decide if they be epitheliomatous, and in these and similar cases of so embryonic a type is the cell overgrowth, that it is impossible for us time after time to declare whether we are dealing with inflammation pure and simple or with actual cancerous tissue. I must confess that when I send in the reports upon such cases I still feel apologetic, I feel that the surgeons and gynæcologists have the idea that a pathologist ought to know these matters and ought to be able to give an assured diagnosis. I feel that the said surgeons and gynæcologists will when they read such reports complain that after

all I, the pathologist, am a very weak reed to have to lean upon. And I am glad that now, when I have no doubtful specimen before me to report upon, I can point out to the surgeons and the gynæcologists the state of affairs as it actually is, namely, that it is at times impossible to distinguish between chronic inflammatory and malignant tissue. And the reason, gentlemen, why it is impossible thus to distinguish between the two is that the difference between them is purely one of degree.

There can be no doubt that at times this inflammatory hyperplasia of gland cells—this development of embryonal or sub-adult gland tissue—passes on imperceptibly into cancer. Although it may be urged that in all cases of cancer the history of previous chronic inflammation cannot be obtained, this fact that antecedent chronic inflammation at times either escapes detection or is not present, in nowise weakens what is here stated, namely, that many cases of chronic irritation and long continued inflammation of moderate intensity, affecting epithelial and glandular tissues merge into carcinomatous manifestations. And so far as I can see, the line separating the one condition from the other, is that which separates continent from incontinent cell growth. In chronic inflammation as seen, for example, at the edge of an ulcer we have a condition of increased blood supply and increased nutrition, and as a result we obtain that cell proliferation already described, associated with reversion to embryonic character, or almost I might state it otherwise and say, that we have reversion to embryonic character with associated embryonic powers of rapid cell multiplication, for the two conditions are inseparable. The only distinction between the inflammatory and the cancerous growth is this, that in chronic inflammation remove the cause of the irritation and the process of abnormal cell growth comes to an end. In cancer, the cells from frequent and rapid multiplication in a more or less embryonic state have gained the habit of growth, of unrestrained growth. It may be also that the vessels going to the region, from long dilation remain distended or have acquired persistent distension; so that even when the primary irritant is removed the part continues to receive nourishment in excess of physiological needs. This, together with paralysed nerve control, may well be factors leading to the first mentioned condition, but before all, it seems to me, that there is to be recognized this assumption of the habit of growth, so that once fully started upon the road of proliferation the cells continue to multiply utterly irrespective of the needs of the organism.

It may be said that this is an assumption on my part, and not

necessarily on the part of the cells, but I would ask you to consider a little before arriving at such a conclusion. The cells of the body, we know, are capable of acquiring other habits ; we know for example that they can acquire a tolerance for sundry drugs ; we believe also now-a-days that acquired immunity for disease is essentially due to the acquirement of another habit, to the accustomance on the part of these cells to the presence of small or weak doses of the products of pathogenic micro-organisms, resulting in the descendants of these cells at a later date being able to withstand, if not actually to be attracted to the products of these same bacteria when present in a more concentrated form. But apart from this support from analogy which, it may be said, is at the most doubtful, we have in the cancer cells clear indications of the assumption of this habit. There is in the first place the undoubtedly embryonic appearance in the cells. Now it is during embryonic life where, under physiological conditions, the cells possess this appearance, that they possess also most characteristically the power of frequent multiplication, that they possess very clearly a physiological habit of growth. Again there is to be noticed the excessive amount of nuclear chromatin. This increase in the amount of chromatin in the nuclei is under ordinary physiological conditions an indication that the cells are undergoing, or are about to undergo, multiplication. In an ordinary cancer, what immediately strikes us, is that all the cells in an alveolus, more especially towards the growing edge of the cancer mass, show a peculiarly intense nuclear staining. Thirdly, the irregular character of the mitosis or indirect cell division observable in cancer cells may in itself be accepted as an indication that the impulse towards division is so strong that the nuclear masses often break into three stars instead of two, or throw off redundant masses. And lastly, what may be termed the intense vitality of the cancer cells is again a character of young growing cells.

It is common to speak of the cells of malignant tumours as being endowed with low vitality. Nothing can be more incorrect. It is indeed true that the more internally situated cells of a new growth exhibit frequent evidence of either necrosis or various forms of degeneration. But those changes are surely to be ascribed not to the lack of vitality of the cells, but to the serious disturbance to the blood supply of the central region of a tumour which almost inevitably follows its eccentric growth. That growth and extension in spite of the pressure of the surrounding organs must also be associated with pressure effects upon the nutrient vessels of the more central area. Compare the cancer cells with those of the surrounding tissues. The latter certainly undergo necrosis and absorption, while the invading

cancer cells show every sign of active growth. The power that these cancer cells have for multiplying in new environment is in itself an evidence of heightened vitality.

It is true that there are certain layers of cells in the normal body which possess a somewhat closely allied intense vitality. The botanists have for long recognized the existence of similar layers in the higher plants and have spoken of them as the "cambium" or cambium layer. I do not know whether with the advance of the gentle science any other name has been given to the strata of the permanently embryonal cells. It would be well if in physiology we had some term denoting the collections of cells of this nature. It is owing to the existenee of these cell layers that we are able to transplant skin and periosteum. In the former the layer in question is the lowest layer of the stratum Malpighi, which throughout life exists in a permanent embryonal condition and which is constantly presenting cell division, and developing new individuals to help to form the epidermis and to replace the scales of dead cells that are constantly being thrown off. In the latter also we have present an analogous layer of permanently embryonal cells. These layers may be said to present throughout life the habit of growth, and it is interesting to notice how peculiarly liable these very cell layers are to become the seat of unrestrainable or unrestricted growth, to manifest malignancy. But under physiological stimuli this excessive growth does not show itself, and under physiological conditions when transplanted, while the vitality of these cells is sufficient to permit of their proliferation when placed in similar environment, when placed in abnormal environment they die, just as any other healthy tissue dies and is absorbed when it is transplanted either subcutaneously or intraperitoneally into another individual. The cancer cells accompanying this power of unrestricted growth have a vitality so intense that when transplanted into widely different regions of the host from the original primary seat of growth they still are able to proliferate, and indeed this intense vitality renders it not impossible that occasionally cancer cells transplanted from one individual may grow in another; but it must be remembered that it is wise not to regard this as a phenomenon of true infection, any more than it is wise to consider the grafting of skin from one individual to another a true infection.

Finally, let me say that that theory is most worthy of acceptance which while being the simplest embraces and explains the largest number of phenomena. As I have shown, the parasitic theory is too limited to be satisfactory. Parasites may possibly be one cause of

chronic irritation and of originating the habit of incontinent cell growth. At most they are one cause ; and till their life history has been mastered, till they are found in every cancerous specimen examined with sufficient care, they cannot be regarded as explaining every case of carcinoma.

The theory held by not a few that a weakening of the basement membrane lining the stratum Malpighi and gland alveoli is to be considered as explaining why the epithelial and gland cells invade the surrounding structures, is unsatisfactory in that it is only applicable to carcinomata, and has no bearing upon the development of malignant connective tissue growths. It is unsatisfactory, again, because we cannot recognize the actual point of weakening of the membrane. We can and must recognize on the other hand the condition of intense and active growth of the cancer cells and of the pre-cancerous cells, if I may so describe them. And it is not difficult to assume that the very intensity of this growth, coupled with the vitality of the new cells which does not permit them to undergo easy atrophy, so long as there is abundant nutrition, is capable of causing so much pressure within the gland alveoli that the weakening of the basement membrane is purely secondary to the vigorous cell growth, so that this habit of growth can explain alone the bursting of the cancer cells through the membrane and their invasion of the adjacent lymphatics.

The theory of a seminium as started by Virchow and elaborated by Creighton and others, while very taking, requires if pushed to its logical conclusion a seminium or seminal invasion for every proliferating cell in the body. True, each of us as a result of the habit of growth of one cell may be regarded as a motile tumour, and certainly in our case there was a primary seminium starting the growth, nevertheless comparative studies show that such is not necessary for the development of every organism or even for the development of sundry organisms high up in the scale of animal life. Add to this that the specific seminium in cancer has never been discovered.

Cohneim's celebrated theory has been so twisted about by various writers upon carcinoma, and has been made to do such yeoman service that it is necessary that I should here refer to it. But the embryonal cell vestiges upon which it is based are only useful in their restricted sense as explaining the rarer forms of cancer in which the condition of glandular or epithelial malignant growth apparently originates in tissues containing normally no glandular or epithelial substances. In its wider application it harmonises with the theory that I have placed before you, inasmuch as it demands as the initial stage of cancer growth the existence of embyronic cells.

It will be seen that the theory that I have laid before you by granting to the cancer cells the habit of tenacious and incontinent growth explains the assumption by the cancer cells of embryonal characters, explains also the overgrowth of these cells, the bursting through the basement membrane, the growth along surrounding lymph spaces, and even in the course of the blood vessels, and, with this, growth similar in character to the primary development at a distance from the primary seat, and so explains the formation of metastases, in fact the theory includes and explains all the essential characters of malignancy.

So far in laying before you these suggestions upon the nature of malignant growth, I have dwelt more especially upon the influence of chronic inflammation of moderate intensity in leading up to neoplastic tissue formation. But it may well be asked if it is necessary to assume that chronic inflammation of moderate intensity is the sole factor to be recognized as originating the habit of incontinent growth. A theory starting from the ground that malignant growth is always preceded by a stage of long continued slight inflammation is indeed untenable, clinical evidence does not warrant a premise of this nature. The most that can be said is that, comparing the histories we obtain in connection with the development of malignant neoplasms which are visible and more or less superficial, with those obtainable in connection with cancer and sarcomata of deep seated organs, we find a very much greater proportion of statements of previous injury and of chronic irritation in the former than in the latter class. I need but call your attention to the almost constant history of irritation obtainable in cases of cancer of the lips or of the tongue, and recent studies would indicate that—in the case of cancer of the breast for example—the more fully the previous history of the patient is studied the more frequently do we obtain evidences of injury inflicted upon the region which has become the primary focus of cancer. (Here, however, it is to be noted that the injury may have been inflicted long years previously.) But granting all this there remain cases in which it is not possible to demonstrate the previous action of chronic irritation, and these cases are sufficiently numerous to render it, I hold, unsafe to attempt to employ the argument by analogy and to assume that though unnoticed there did exist a pre-cancerous irritative stage.

If we examine the conditions associated with slight chronic irritation we cannot fail to notice that with the overgrowth of the tissues there is an accompanying condition of increased nutrition. Take for instance the edge of a chronic ulcer. The zone of the increased epithelial and connective tissue growths is at the same time a zone of

dilated vessels. That dilatation and the increased blood flow in the region may safely be said to have been brought about not so much by the demands of the peripheral tissue as by the central irritation, or in other words it would seem that, as a consequence of focal irritation, there is induced a dilatation of the vessels and increased blood flow extending beyond the area directly affected by the irritant. If this be so (and there is much to be said in favour of the view) then not a little of what are regarded as the effects of chronic irritation of a mild type may rather be assigned more immediately to over-nutrition —to a blood supply beyond the physiological needs of the region. And other cases in which there is such nutrition in excess of physiological needs unassociated with inflammation may likewise tend to the development of neoplastic growths.

We here approach a department of pathology that has been little worked at, and I must needs speak with caution. Indeed I would only hint that very possibly after the climacteric when retrogression of certain issues becomes increasingly manifest, with the absorption of certain of the components of sundry tissues other components of these same tissues gain a relatively greater amount of nourishment, and more especially where by injury (it may have been years previously) a certain amount of deformity or altered relationship of parts, a certain amount of instability, has already been introduced, there we have an association of factors peculiarly favourable to the acquirement of a tendency towards irregular and sub-adult cell growth —of a tendency towards the assumption by sundry cells of the aforesaid habit of incontinent growth. While upon this subject, upon the liability of cancerous growth to occur at or about the climacteric, I may point out that the cell changes accompanying the involution of the tissues at the change of life are reversionary in character, they resemble to a certain extent the changes which I have described as accompanying chronic inflammation.

Before closing this paper, I must needs impress upon you that there is one factor which I have not touched upon, namely, modified nerve control over the tissue. This may be a factor in the development of neoplasms, but beyond the fact that recent observations seem to be proving more and more conclusively the intimate relationship between the nervous system and the fixed cells of the body, there is nothing that can safely be said with regard to the matter; there are no experiments or direct observations at all bearing upon it. It is safer, therefore, not to do anything beyond referring to its very possible existence, and pointing out that it is wise not to leave it wholly out of account.

To return now to the substance of my opening remarks. If the suggestions (and I hardly like to venture to call them more than suggestions) which I have thrown out have any solid basis, then it would appear probable that the advance in interference with cancer must proceed directly along the lines that it is at present taking in the hands of the surgeons, namely, the duty of the surgeon must be to recognise the existence of new cell growths at the very earliest moment, and more, now that operation is so robbed of its previous terrors, and that parts can be removed with so little disfigurement and so little danger of sequelæ, it becomes the duty of the wise surgeon to remove every neoplasm, benign as well as malignant, at the first opportunity. There is no valid reason for retention, there is the possibility, even if it be but distant, that the benign growth may assume malignant properties. Destruction of the cancerous tissue at the earliest moment, whether by the knife or by the administration of substances which excite a specific action upon the cells,—this alone, I cannot but hold, is what we have to recognize as the procedure at which to aim.